Response

Claims 30-51 of the subject application are pending. Applicant has amended claim 1 and has not deleted or added any claims. Accordingly, claims 30-51 are presently being examined.

In view of the following Response, applicant respectfully requests that the Examiner reconsider and withdraw the rejections made in the outstanding Office Action.

Support for the Amendment

Applicant has amended the claims in order to more clearly describe and distinctly claim the subject matter of applicant's novel method for treating a pulmonary disease state in mammals by protecting indigenous *in vivo* levels of nitric oxide in mammalian cells. Specifically, applicant has amended claim 30 to recite "during ozone inhalation above ambient levels". This claim is supported in applicant's specification at, for example, page 2, lines 19-30. Ambient levels are known to one of skill in the art and are, for example, set out in the reference cited by the Examiner, Concise Encyclopedia of Chemistry, p. 770, col. 2.

These amendments to the claims are fully supported in the specification as originally filed. Thus no new matter is introduced by these amendments in accordance with 35 U.S.C. §132. Accordingly, applicant requests entry of these amendments.

Rejection of Claims 30-51 on the Grounds of Nonstatutory Obviousness-type Double Patenting over *Martin'810, Katz'723*, and *Martin'354*

The Examiner has rejected claims 30-51 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of United States Patent no. 6,689,810 (*Martin'810*). The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the present application teaches a method for treating a pulmonary disease state in a mammal by protecting indigenous *in vivo* levels of nitric oxide in mammalian cells during ozone inhalation comprising

contacting the mammalian cells with a therapeutically effective amount of a nitric oxide mediator, wherein the nitric oxide mediator is selected from the group consisting of pyruvates, pyruvate precursors, α-keto acids having four or more carbons atoms, precursors of α-keto acids having four or more carbon atoms, and the salts thereof; and the patented application teaches a method for treating a pulmonary disease state in mammals by altering indigenous *in vivo* level of nitric oxide in mammalian cells comprising contacting the mammalian cells with a therapeutically effective amount of a nitric oxide mediator, wherein the nitric oxide mediator is selected from the group consisting of pyruvates, pyruvate precursors, α-keto acids having four or more carbons atoms, precursors of α-keto acids having four or more carbon atoms, and the salts thereof.

The Examiner has further rejected claims 30-32 and 35-51 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 of United States Patent no. 6,623,723 (*Katz'723*). The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the present application teaches a method for treating a pulmonary disease stated in a mammal by protecting indigenous *in vivo* levels of nitric oxide in mammalian cells during ozone inhalation comprising contacting the mammalian cells with a therapeutically effective amount of a nitric oxide mediator, wherein the nitric oxide mediator is selected from the group consisting of pyruvates, pyruvate precursors, α-keto acids having four or more carbons atoms, precursors of α-keto acids having four or more carbon atoms, and the salts thereof; and the patent teaches a method for treating bronchial constriction and a method for treating airway diseases with a compound selected from the group consisting of pyruvate and pyruvate precursors that are administered by inhalation.

The Examiner has still further rejected claims 30 and 33-51 as provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending United States Patent application no. 10/205,354 (*Martin'354*). The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the present application teaches a method for treating a pulmonary disease stated in a mammal by protecting indigenous *in vivo* levels of nitric oxide

in mammalian cells during ozone inhalation comprising contacting the mammalian cells with a therapeutically effective amount of a nitric oxide mediator, wherein the nitric oxide mediator is selected from the group consisting of pyruvates, pyruvate precursors, α-keto acids having four or more carbons atoms, precursors of α-keto acids having four or more carbon atoms, and the salts thereof; and the copending patent application teaches a method for treating bronchial constriction and a method for treating airway diseases with an α-keto acid, α-butyric acid, α-keto-adipic acid, α-keto-caproic acid, α-keto-isovaleric acid, their salts and mixtures thereof that are administered by inhalation.

The Examiner states that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. The Examiner argues that claims 30-51 stand provisionally rejected under the judicially created doctrine of double patenting and 35 U.S.C. §101 as claiming the same invention as that of the claims of *Martin'810, Katz'723*, and *Martin'354*.

The Examiner states that applicant argues that its invention claimed in the present application is patentably distinct from the inventions articulated in *Martin'810, Katz'723*, and *Martin'354* because none of these cases recite the limitation "during ozone inhalation" in association with their inventions, as the present application does. The Examiner argues that applicant fails to factually analyze how the recitation of "during ozone inhalation" in its claims distinguishes them and thereby, makes its invention distinct. Moreover, the Examiner states that applicant has failed to provide any facts to support the assertion that lack of the phraseology "during ozone inhalation" in *Martin'810, Katz'723*, and *Martin'354* means, in fact, that ozone is not inhaled. The Examiner argues that it is known by those of skill in the art that ozone is present in the atmosphere and as a result, inhaled on some level at all times. See Concise Encyclopedia of Chemistry, p. 770, col. 2). Applicant's amendments to the claims obviate the Examiner's nonstatutory obviousness-type double patenting rejection.

As set out above, applicant has amended claim 30 to recite "during ozone inhalation above ambient levels".

Martin'810, Katz'723, and *Martin'354* do not recite "protecting indigenous *in vivo* levels of nitric oxide in mammalian cells "during ozone inhalation above ambient levels". Applicant's recite in the specification as follows:

> H_2O_2 is the oxygen radical that appears to have the major effect on airway tone and causes contraction in both bovine and guinea pig airways. (14,15). H_2O_2 markedly potentiates the cytotoxic effects of eosinophil derived enzymes such as 5,8,11,14,17-eicosapentaenoic acid (16). Excess superoxide anions and hydrogen peroxide, produced during the inflammatory phase of an injury, will destroy healthy tissue surrounding the site and will mitigate the positive bronchodilation effect of nitric oxide (26). Oxygen radicals can also initiate lipid peroxidation employing arachidonic acid as an substrate producing prostaglandins and leukotrienes. H_2O_2 can induce arachidonic acid metabolism in alveolar macrophages (17,26). Oxygen radicals also produce 8-isoprostanes, which are potent renal and pulmonary artery vasoconstrictors, bronchoconstrictors, and induce airflow obstructions (26, 27). (emphasis added, applicant's specification at page 2, lines 19-30).

As set out above, applicant's "during ozone inhalation" refers to inhalation of ozone above ambient levels. Ambient levels of ozone are known to one of skill in the art and are, for example, set out in the reference cited by the Examiner, Concise Encyclopedia of Chemistry, p. 770, col. 2, which states that ozone levels start at 3×10^{-6} vol % at the surface of the earth and reach a maximum of 2×10^{-5} vol % at 20-25 km altitude.

Above ambient levels of ozone refers to levels of ozone where the level is above the "normal" level of ozone for that altitude such as in urban areas where excess ozone is produced by pollution or any other reason. Excess ozone triggers inflammation, trigger asthma, and injures lungs in people with and without lung diseases to produce a lung disease. Pulmonary diseases caused by inhalation of ozone are very different from pulmonary diseases that are regulated or controlled internally and so are their treatments. Ozone inhalation causes damage to tissues, white blood cells, and other cells needed to keep lungs healthy. The inhalation of the α-keto acids in the present invention prevents lung diseases from forming in addition to treating a lung disease. Ozone activates NF Kappa B in normal people with and without lung diseases, to produce lung disease. Applicant's nitric oxide mediators react with

ozone to neutralize it prior to ozone causing lung disease. See copy enclosed, Am. J. Respir. Cell Mol. biol., volume 20, number 5, May, 1999m 1067-1072

Accordingly, the Examiner's rejection of claims 30-51 on the grounds of nonstatutory obviousness-type double patenting over *Martin'810, Katz'723*, and *Martin'354* should be withdrawn.

Rejection of Claims 30-32, 35, and 43-51 as being Anticipated under 35 U.S.C. §102(b) by *Katz'*818, *Katz'*388, *Katz'*459, and *Katz'*384

The Examiner has rejected claims 30-32, 35 and 43-51 as being anticipated under 35 U.S.C. §102(b) by WO97/10818 (*Katz'*818), United States Patent no. 5,798,388 (*Katz'*388), United States Patent no. 5,939,459 (*Katz'459*), and United States Patent no. 5,952,384 (*Katz'*384). The Examiner states that the four *Katz* references (collectively referred to as "*Katz*") teach methods and compositions for treating a disease state in a mammal caused by inflammatory response and teach the disease state is treated with an inflammatory mediator. The Examiner argues that the inflammatory mediator is a compound selected from the group consisting of a pyruvate or a pyruvate precursor and the pyruvates are the same as the applicant's preferred pyruvates and the pyruvate precursors. The Examiner maintains that the references disclose the disease state treated is an airway disease, such as emphysema, cystic fibrosis, acute bronchiectasis, and asthma, are all encompassed by the applicant's pulmonary disease state of claim 30. The Examiner states that the references teach the inflammatory mediator may be administered prior to, after and/or with other therapeutic agents and the additional therapeutic agents are antibacterials, antivirals, antifungals, antihistamines, proteins, enzymes, hormones, nonsteroidal anti-inflammatories, cytokines and steroids. The Examiner also states that the references teach the inflammatory mediator can be administered prior to, concomitantly, and after administration of the inflammatory mediator and that the inflammatory mediator (nitric oxide mediator) can be administered alone or in combination with other therapeutic agents administered by inhalation.

The Examiner further states that the nitric oxide mediator in the instant application comes within the purview of an "inflammatory mediator" noted in *Katz*. The Examiner states

that *Katz* defines pyruvates and pyruvate precursors as inflammatory mediators while the present invention defines pyruvates and pyruvate precursors as nitric oxide mediators. The Examiner contends that while the terminology may differ slightly, the functionality of both the nitric oxide mediators in the instant application and the inflammatory mediators in *Katz* are identical. The Examiner argues that an alteration in the label of either has no impact on their chemical and physiological properties and effects and as is well known by those of ordinary skill in the art, nitric oxide effectively kills microorganisms, but is ineffective when impacted adversely by the presence of oxygen radicals. The Examiner states that an over-saturation of microorganisms creates infection and disease, which in turn, can cause inflammation. The Examiner concludes that pyruvates and pyruvate precursors, acting as inflammatory mediators and nitric oxide mediators, prevent the deactivation of nitric oxide otherwise caused by the presence of oxygen radicals, thereby enabling a stabilized form of nitric oxide, which effectively kills microorganisms and thereby treats illnesses and diseases caused thereby.

The Examiner states that although anticipation does require that prior art forming the basis for a 35 U.S.C. §102(b) rejection contain art in a single reference that meets each and every functional limitation set forth in an applicant's claim. The Examiner states that *Katz* collectively, and *Katz*'388, *Katz*'459, and *Katz*'818, individually meet the limitations set forth in claims 30-32, 35, and 43-51. Applicant's claims as amended obviate the Examiner's rejection.

As set out above, applicant has amended claim 30 to recite "during ozone inhalation above ambient levels".

In summary, *Katz*'818, *Katz*'388, *Katz'459*, and *Katz*'384, do not teach applicant's method for "treating a pulmonary disease state in mammals by protecting indigenous *in vivo* levels of nitric oxide in mammalian cells during ozone inhalation above ambient levels". Pyruvate enhances nitric oxide availability to effect bronchodilation by protecting it from oxygen radicals, enhancing its synthesis, and by regulating its effect intracellularly and thus maintaining appropriate cellular levels and functions for nitric oxide. In one embodiment, applicant's method can treat levels of nitric oxide in the mammalian cells that are abnormally

low in the disease state. In another embodiment, applicant's method can treat the levels of nitric oxide in the mammalian cells that are abnormally high in the disease state.

The present application provides certain α-keto acids that have unique properties to up or down regulate the inflammatory process thus regulating the healing process (reepithelization) including the treatment of lungs that inhale ozone. Excess ozone is detrimental to healing and can injure drugs designed to fight infections. The ability to neutralize ozone is useful in these cases. The use of these α-keto acids in combination is unique. None of the *Katz* patents disclosed the use of α-keto acids in combination to regulate different aspects of the inflammatory process and healing due to ozone damage. Applicant's α-keto acids react directly with ozone that controls the inflammatory process.

The proper use of α-keto acid combinations can control the inflammatory process, thus enhance the healing process, fight infections and protect drugs from ozone, giving antimicrobial agents a longer time to kill infections and prevent a lung disease from occurring especially in young children.

Each α-keto acid has its unique breakdown products that react differently to produce different results. The breakdown products also have different solubilities and hence act on different parts of the cell. The more water-soluble α-keto acids penetrate the cytosol of the cell while the α-keto acids containing C_6 and up are more fat-soluble and penetrate into membranes. Each α-keto acid has its own unique transport system and its own metabolic pathway in the cell. As set out in Table 1 in applicant's specification, each α-keto acid acts differently. For example, α-keto butyrate was the poorest in healing when compared to the other α-keto acids. Some of the α-keto acids were irritating and some were not irritating. In short, each α-keto acid acts differently on a wound. One cannot predict success based on structure alone.

The *Katz'818* reference discloses a method for treating a disease state in mammals caused by mammalian cells involved in the inflammatory response comprising contacting the mammalian cells with an inflammatory mediator wherein the inflammatory mediator is present in an amount capable of reducing the undesired inflammatory response and is an antioxidant.

The *Katz'388* reference discloses a method for treating asthma in mammals caused by mammalian cells involved in the inflammatory response comprising contacting the mammalian cells with an inflammatory mediator; wherein the inflammatory mediator is selected from the group consisting of pyruvate and a pyruvate precursor and is present in an amount capable of reducing the undesired inflammatory response antioxidant provided that said pyruvate or pyruvate precursor is not administered together with albuterol.

The *Katz'459* reference discloses a method for treating emphysema in mammals caused by mammalian cells involved in the inflammatory response comprising contacting the mammalian cells with an inflammatory mediator wherein the inflammatory mediator is present in an amount capable of reducing the undesired inflammatory response and is an antioxidant.

The *Katz'*384 reference discloses a method for treating airway disease in mammals caused by mammalian cells involved in the inflammatory response comprising contacting the mammalian cells with an inflammatory mediator wherein the inflammatory mediator is present in an amount capable of reducing the undesired inflammatory response and is an antioxidant.

The present invention provides methods for treating a pulmonary disease state in mammals by protecting indigenous *in vivo* levels of nitric oxide in mammalian cells during ozone inhalation above ambient levels comprising contacting the mammalian cells with a therapeutically effective amount of a nitric oxide mediator, wherein the nitric oxide mediator is selected from the group consisting of pyruvates, pyruvate precursors, α-keto acids having four or more carbon atoms, precursors of α-keto acids having four or more carbon atoms, and the salts thereof..

Nitric oxide is known to kill bacteria, viruses, funguses, and tumors, however, nitric oxide can be damaged by oxygen radicals and thus will not be effective. Nitric oxide mediators such as pyruvates and α-keto acids can protect nitric oxide from oxygen radicals and permit nitric oxide to better treat bacterial infections, viral infections, fungal infections, and tumors. The pulmonary tumors suitable for treatment include epidermoid (squamous cell) carcinoma, small cell (oat cell) carcinoma, adenocarcinoma, and large cell (anaplastic) carcinoma. Nitric oxide mediators can protect naturally produced nitric oxide as well as nitric

oxide co-administered with the nitric oxide mediator. The nitric oxide mediator may be administered prior to administration of the nitric oxide source, concomitantly with administration of nitric oxide source, or administered after administration of nitric oxide source. Nitric oxide is generally administered as a gas and so will be very effective in the lungs and sinuses. In many cases, pulmonary diseases produce infections that this nitric oxide mediator/nitric oxide combination can treat. The nitric oxide mediator may be inhaled first to eliminate hydrogen peroxide followed by inhalation of nitric oxide, which would not then be destroyed, by hydrogen peroxide. The nitric oxide mediator/nitric oxide combination would be especially effective for treating pulmonary diseases such as bronchial asthma, acute bronchitis, emphysema, chronic obstructive emphysema, centrilobular emphysema, panacinar emphysema, chronic obstructive bronchitis, reactive airway disease, cystic fibrosis, bronchiectasis, acquired bronchiectasis, kartaagener's syndrome, acelectasis, acute atelectasis, chronic acelectasis, pneumonia, essential thrombocytemia, legionnaire's disease, psittacosis, fibrogenic dust disease, diseases due to organic dust, diseases due to irritant gases and chemicals, hypersensitivity diseases of the lung, and idiopathic infiltrative diseases of the lungs. (applicant's specification at page 8, lines 1-26).

In one embodiment, the levels of nitric oxide in the mammalian cells are abnormally low in the disease state. In another embodiment, the levels of nitric oxide in the mammalian cells are abnormally high in the disease state. Whether the levels of nitric oxide are abnormally low or abnormally high can be determined from the level of nitric oxide a patient exhales. Knowing what a patient exhales determines the dose of nitric oxide the patient receives. Normal lung levels of nitric oxide are 2-10ppb. In the sinus area, the levels of nitric oxide are 1000x that ranging from 1-30ppm. Macrophages produce 100-500 ppb to kill bacteria. People with normal levels of nitric oxide exhale 2-5ppb. Asthmatics exhale 5-100 times that level, i.e., 100-300ppb. Patients with adult respiratory distress syndrome (ARDs) are treated with 10-30ppm. Excess nitric oxide in excess of 50ppm will react with H_2O_2 to produce NO_2, which is toxic. Nitric oxide does not produce cancer. The normal volume of nitric oxide used is 20ppm times 30 minutes. (applicant's specification at page 11, lines 4-16).

In a preferred embodiment, the method may further comprise contacting the mammalian cells with a nitric oxide source selected from the group consisting of nitric oxide,

nitric oxide precursors, nitric oxide stimulators, nitric oxide donors, and nitric oxide analogs. Preferably, the nitric oxide source is nitric oxide. Preferably, the nitric oxide precursor, nitric oxide stimulator, nitric oxide donor, or nitric oxide analog is selected from the group consisting of L-arginine, ADP, arachidonic acid, nitrogylcerin, nitroprusside, Sin-1 and SNAP. More preferably, the nitric oxide precursor, nitric oxide stimulator, nitric oxide donor, or nitric oxide analog is L-arginine. (applicant's specification at page 11, line 38, to page 12, line 7).

Nitric oxide is preferably employed as a gas that is nebulized to assure that proper amounts are delivered. Nitric oxide may be placed in an inert formula. The preferred route of administration is by inhalation. In a preferred embodiment, a sterile solution of nitric oxide mediator and/or nitric oxide source is nebulized and inhaled by the patient. A therapeutically effective amount of nitric oxide mediator and/or nitric oxide source is inhaled. This may be accomplished in a single inhalation or by repeated inhalations over a period of time typically 1 to 30 minutes. Preferably, inhalation will be complete in less than 20 minutes. Most preferably inhalation will be complete in less than 15 minutes. Patients with adult respiratory distress syndrome are generally given nitric oxide for 30 minutes at 20ppm. Patients with adult respiratory distress syndrome may also be given nitric oxide for 7 hours or several days at 2ppm in a tent or with a mask. (applicant's specification at page 19, lines 20-31).

Pyruvate controls the positive and negative effects of nitric oxide at higher levels. Too high a level of nitric oxide is detrimental to cells. Pyruvate will protect cells from excess nitric oxide and this explains its effect on mild asthmatics. Moderate to severe asthmatics and emphysema patients produce much higher levels of oxygen radicals especially in smokers, and it would be expected that higher levels of pyruvate would produce better results in these patients. The ability to control the levels of nitric oxide is important. Over production or under production is detrimental and produces various diseases in both the lungs and nasal cavities. Pyruvate, at 0.5mM levels, protects nitric oxide and can be used in diseases where nitric oxide production is low, i.e., in smokers, mild asthmatics, in intubated or tracheostomized patients, in normal subjects after exercise and hyperventilation, COPD patients, and in patients with cystic fibrosis. In asthmatics, exhaled nitric oxide levels are significantly elevated prior to an attack, then the exhaled nitric oxide levels are significantly

reduced by 20-40% immediately after a 20% fall in FEV1 by histamine, AMP, or hypertonic saline challenge in steroid naive asthmatic subjects. Patients who produce excess nitric oxide include those with kartagener's syndrome, moderate or severe asthma, sarcoidosis, and fibrosing alveolitis. Increased nitric oxide levels are chemotactic for eosinophils, which produce and enhance inflammation. Eosinophils affects dyspnoea perception in asthma by releasing neurotoxins. Inhaled B2 agonists do not have any effect on nitric oxide production and this presumably affects their lack of effect on chronic inflammation in asthma. Acute treatment with corticosteriods during an exacerbation of asthma is associated with a decline in nitric oxide values in adults and children. Nitric oxide is elevated in the nasal cavities of healthy newborns and in healthy adults. Nitric oxide is markedly reduced in the nasal cavities of children suffering from cystic fibrosis, and in patients with chronic sinusitis, allergic rhinitis, with respiratory disorders and pre-eclampsia. When inhaled, nasally derived nitric oxide reaches the lower airways and the lungs, and nitric oxide may be involved in the regulation of pulmonary functions and primary host defenses. (applicant's specification at page 20, line 20, to page 21, line 10).

Excess sodium pyruvate beyond that needed to neutralize oxygen radicals will enter the bronchial and lung cells. All cells have a transport system that allow cells to concentrate pyruvate at higher concentrations than serum levels. In the cell, pyruvate raises the pH level, increases levels of ATP, decreasing levels of ADP and cAMP, and increases levels of GTP, while decreasing levels of cGMP. Nitric oxide acts in the opposite mode by increasing levels of cGMP and ADP, and requires an acid pH range in which to work. Generally, the body will make normal levels of pyruvate but will produce higher levels in response to NO_2, which is produced, from nitric oxide and H_2O_2. (applicant's specification at page 21, lines 12-20).

In summary, pyruvate enhances nitric oxide availability to effect bronchodilation by protecting it from oxygen radicals, enhancing its synthesis, and by regulating its effect intracellularly and thus maintaining appropriate cellular levels and functions for nitric oxide. Nitric oxide is therapeutically effective in patients with adult respiratory distress syndrome and in patients with persistent pulmonary hypertension of neonates because both diseases produce severe hypoxemia (reduction of oxygen, deficient oxygenation), which inhibits the production of oxygen radicals that can react with nitric oxide to produce NO_2, which is known

to induce acute lung injury. In patients with COPD, nitric oxide treatment has not produced efficacious results because most COPD patients produce oxygen radicals that react with nitric oxide to produce NO_2. Combining the inhalation of nitric oxide with pyruvate would produce the desired effect, enhancing the efficacy of an approved drug. This combination can be used in the lungs or in the nasal cavities where low production of nitric oxide is found. Nitric oxide is also a natural antimicrobial agent used to kill invading microorganisms. The combination of pyruvate and nitric oxide is effective for the treatment of tumors, bacterial infections, fungal infections, viral infections, angina, ischemic diseases, and congestive heart failure. In diseases where overproduction of nitric oxide is detrimental, excess pyruvate can be used alone to lower nitric oxide synthesis. Excess pyruvate is sufficient pyruvate to neutralize H_2O_2 and to enter the cell to counter the effects of nitric oxide. Excess pyruvate acts in the opposite direction of nitric oxide. (applicant's specification at page 22, line 22, to page 22, line 4).

Under 35 U.S.C. §102, anticipation requires that each and every element of the claimed invention be disclosed in the prior art. *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987). Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984) (emphasis added). We think the precise language of 35 U.S.C. §102 that "a person shall be entitled to a patent unless," concerning novelty and unobviousness, clearly places a burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under §102 and §103. *In re Warner*, 154 USPQ 173, 177 (C.C.P.A. 1967), cert. denied, 389 U.S. 1057 (1968).

Accordingly, the Examiner's rejection of claims 30-32, 35, and 43-51 as being anticipated under 35 U.S.C. §102(b) by *Katz'*818, *Katz'*388, *Katz'*459, and *Katz'*384 should be withdrawn.

Rejection of Claims 30 and 33-51 under 35 U.S.C. §103(a) as being unpatentable over *Fink et al.* in view of *Radhakrishnan et al.*

The Examiner has rejected claims 30 and 33-51 under 35 U.S.C. §103(a) as being unpatentable over WO02/074301 A1 (*Fink et al.*) in view of United States patent no. 5,192,528 (*Radhakrishnan et al.).* The Examiner states that *Fink et al.* teaches the use of α-ketoalkanoic acid or their physiologically acceptable salts, for example, C3-C8 α-ketoalkanoic acids such as α-ketobutyric acid, α-ketopentanoic acid, and α-ketohexanoic acid, for the treatment of cytokine-mediated inflammatory conditions including asthma. The Examiner further states that the instant invention differs from the cited reference in that the reference does not teach the addition of therapeutic agents. The Examiner argues that the secondary reference of *Radhakrishnan et al.* teaches the use of corticosteroid for the treatment of asthma by inhalation. The Examiner concludes that one skilled in the art would have assumed the combination of two individual agents would provide the additive effect in the absence of evidence to the contrary. The Examiner argues that the instant invention differs from the cited references because *Fink et al.* does not teach that the dosage forms can be administered by inhalation and the specific dosage amounts. Nevertheless, the Examiner maintains that one skilled in the art could have readily optimized the effective dosage forms and the manner of administration.

The Examiner further states that applicant argues that although *Fink et. al.* do disclose a composition that may include α-ketoalkanoic acid, physiologically-acceptable salts, esters, and amides thereof, the examples provided therein are limited to the use of ethyl pyruvate and how the use of ethyl pyruvate differs from the pyruvates taught in the current application. The Examiner argues that discussion on why ethyl pyruvate was not a pyruvate contemplated in the current application is improper for two reasons. First, the Examiner states that the claim drawn to pyruvates in the current application was not rejected as being obvious over *Fink et al.* in view of *Radhakrishnan,* and second, even if the pyruvates were pursuant to 35 U.S.C. §103(a), the discussion would potentially be unfounded still, since the enablement or teaching of a subject matter, depending on the subject matter, of course, does not have to

be illustrated by example in a specification to be included as part of the claimed invention. The Examiner states that with regard to α-ketoalkanoic acids, physiologically-acceptable salts, esters, and amides thereof, by applicant's own admission, *Fink et al.* do teach a method of administering a composition containing these compounds. Applicant's claims as amended obviate the Examiner's rejections.

As set out above, applicant has amended claim 30 to recite "during ozone inhalation above ambient levels".

In summary, applicant's claims are not obvious over *Fink et al.* because while *Fink et al.* does disclose compositions comprising α-ketoalkanoic acids including physiologically-acceptable salts of α-ketoalkanoic acid, esters of α-ketoalkanoic acid, and amides of α-ketoalkanoic acid, *Fink et al.* only discloses the use of ethyl pyruvate in his Examples I-VIII. The hydrophobic ethyl pyruvate of *Fink et al.* is NOT a physiologically acceptable salt, ester, or amide. The hydrophobic ethyl pyruvate of *Fink et al.* and the hydrophilic α-keto acids and their salts of applicant are not the same compounds. Hydrophobic pyruvate esters and hydrophilic α-keto acids and their salts are absorbed differently and are metabolized differently. As a consequence, one class of compounds which are administered through one route (oral, intravenous, or topical forms) to treat one disease cannot necessarily be administered through another route (inhalation) to treat another disease. *Fink et al.* does not discuss or teach the use of applicant's specific α-keto acids as antioxidants to neutralize hydrogen peroxide in the lungs of mammals to treat bronchial constriction and bronchial spasms.

During bronchial constriction, the muscles in the bronchial tubes constrict, causing difficulty in breathing. Bronchial constriction is often followed by increased mucous secretions, which further plug the airways. Applicant has found that α-keto acids having four or more carbon atoms, and precursors thereof, act as bronchial dilators in mammals with bronchial constriction. Applicant believes that when an α-keto acid having four or more carbon atoms, or a precursor thereof, is applied to lung tissue, hereinafter the bronchial dilator, the bronchial dilator acts outside of the lung cells. Without being held to a specific theory of operation, applicant believes that the extra cellular bronchial dilators act as a

reactive oxygen species antagonist reducing the active oxygen species present in the lung. Applicant believes these reactive oxygen species are either directly or indirectly responsible for bronchial constriction and bronchial spasm. When the active oxygen agents are removed, the lungs return to normal. During the process of reducing the active oxygen species in the lung, the bronchial dilator is consumed. Bronchial spasm is a series of short duration bronchial constrictions alternating with periods of bronchial relaxation. Additionally, the α-keto acids, and precursors thereof, may act to enhance the lung's ability to remove mucus thereby clearing the lungs allowing less obstructed airflow. The α-keto-acids, and precursors thereof, may reduce the viscosity of mucus by removing hydrogen peroxide, which is known to thicken mucus. The α-keto-acids, and precursors thereof, may also act as surfactants further reducing the viscosity of mucus thus facilitating its removal through the normal bodily processes of expulsion and absorption. The removal of mucus may also reduce the triggers present in the lung thereby reducing and/or preventing bronchial constriction and bronchial spasm. Preferably, the therapeutic compositions are administered by inhalation.

The *Fink et al.* reference discloses a method for ameliorating cytokine effects during inflammation by preventing endotoxin-induced lethality and attenuating the release of "early" tumor necrosis factor (TNF) and interleukin-1β (IL-1β) and "late" high mobility group B-1 (HMGB-1) phase mediators of pathogenic systemic injuries. *Fink et al.* states that the method comprises administering to a patient a composition comprising an α-ketoalkanoic acid including physiologically-acceptable salts of α-ketoalkanoic acid, esters of α-ketoalkanoic acid, and amides of α-ketoalkanoic acid. Suitable α-ketoalkanoic acids include C3-C8 straight chained or branched α-ketoalkanoic acids, such as pyruvic acid, and physiologically acceptable salts of α-ketoalkanoic acids including Na+, K+, Ca++, Mg+, and NH4+. (*Fink et al.* at page 4, line 23 to page 5, line 13). *Fink et al.* states that esters of α-ketoalkanoic acids are preferred, such as pyruvate esters wherein the ester position is alkyl, aralkyl, alkoxyl, carboxyalkyl, glyceryl or dihydroxyacetone. Specific examples include ethyl, propyl, butyl, carboxymethyl, acetoxymethyl, carbethoxymethyl, and ethoxymethyl, with ethyl esters being preferred. (*Fink et al.* at page 5, lines 14-27).

While *Fink et al.* does state that the composition may comprise α-ketoalkanoic acid including physiologically acceptable salts of α-ketoalkanoic acid, esters of α-ketoalkanoic acid, and amides of α-ketoalkanoic acid, Examples I-VIII of *Fink et al.* discuss only the use of ethyl pyruvate.

Fink et al. states that the "therapeutic compositions of the invention may be administered orally, topically (e.g., ointment, gel or cream), or parenterally, (e.g., intranasally, subcutaneously, intramuscularly, intravenously, intraluminally, intra-arterially, intravaginally, transurethrally or rectally) by routine methods in pharmaceutically acceptable inert carrier substances." *Fink et al.* at page 13, lines 15-21. *Fink et al.* does not teach administering the compositions into the lung by inhalation.

First, the ethyl pyruvate taught by *Fink et al.* is hydrophobic and is not transported into the cells via the (hydrophilic) pyruvate transport system. There are no naturally occurring metabolic pathways or transport systems to process esters and amides of α-ketoalkanoic acids. Esters are relatively stable and can disrupt cellular membranes, which accounts for their ability to inhibit secretion of high mobility group B-1 (HMGB-1), *Fink et al.* at page 11, lines 20-30. The stability of ethyl pyruvate in the lungs is also a problem because it defuses into critical lung membranes that are needed for oxygen exchange. Applicant's α-keto acids, on the other hand, are consumed quickly in the lungs.

Second, the use of ethyl pyruvate, the only compound recited in the Examples of *Fink et al.*, in the lungs of patients suffering with lung diseases would result in the reaction of ethyl pyruvate with hydrogen peroxide to produce pyruvate and the toxic by-products, ethyl alcohol and/or ethane. Applicant, on the other hand, teaches the use of α-keto acids which react with hydrogen peroxide to produce carboxylic acids, carbon dioxide, and water, all non-toxic by-products.

Third, *Fink et al.* also does not teach or suggest the use of his compounds for inhalation. Asthma may be treated with various compounds in oral, intravenous, or topical forms but such compounds cannot necessarily be administered by inhalation and may be toxic if inhaled. *Fink et al.* does not discuss or teach the use of applicant's specific α-keto acids as antioxidants to neutralize hydrogen peroxide in the lungs of mammals to treat bronchial

constriction and bronchial spasms. Rather, *Fink et al.* teaches the use of esters and amides of α-ketoalkanoic acids to treat diseases where certain cytokines are produced.

Applicant's therapeutic compositions are administered by inhalation. The therapeutic compositions may be first nebulized by any suitable means. The means of delivering the medicine to the lungs may be for example by nebulizer or metered dose inhalers (MDI's). Such MDI's may use propellants such as gases or they may be dry powder inhalers or mini-nebulizers. The therapeutic compositions may be in liquid or solid form with liquid droplets or particle size being small enough to facilitate access to the bronchi by inhalation. *Fink et al.* does not discuss the use of α-keto acids as inhalants to treat lung diseases and does not determine inhalation concentrations.

Hence, the hydrophobic ethyl pyruvate of *Fink et al.* and the hydrophilic α-keto acids and their salts of applicant are not the same compounds. Hydrophobic pyruvate esters and hydrophilic α-keto acids and their salts are absorbed differently and are metabolized differently. As a consequence, one class of compounds which are administered through one route (oral, intravenous, or topical forms) to treat one disease cannot necessarily be administered through another route (inhalation) to treat another disease.

The *Radhakrishnan et al.* reference discloses a method for administering a therapeutic dose of a corticosteroid to the respiratory tract, for treatment of a condition or disease of the respiratory tract. The method comprises (a) preparing an aqueous suspension of liposomes having sizes less than about 0.5 microns and containing the corticosteroid in entrapped form; (b) aerosolizing the suspension in a pneumatic nebulizer under conditions which produce aerosol particle sizes in the range between about 0.4 and 6 microns, favoring aerosol particle deposition in the respiratory tract; and (c) administering by inhalation, a quantity of the aerosol containing such therapeutic dosage of the corticosteroid in liposome-entrapped form.

As set out above, applicant's claims are not obvious over *Fink et al.* because while *Fink et al.* does disclose compositions comprising α-ketoalkanoic acids including physiologically-acceptable salts of α-ketoalkanoic acid, esters of α-ketoalkanoic acid, and amides of α-ketoalkanoic acid, *Fink et al.* only discloses the use of ethyl pyruvate in his Examples I-VIII. The hydrophobic ethyl pyruvate of *Fink et al.* is NOT a physiologically

acceptable salt, ester, or amide. The hydrophobic ethyl pyruvate of *Fink et al.* and the hydrophilic α-keto acids and their salts of applicant are not the same compounds. Hydrophobic pyruvate esters and hydrophilic α-keto acids and their salts are absorbed differently and are metabolized differently. As a consequence, one class of compounds which are administered through one route (oral, intravenous, or topical forms) to treat one disease cannot necessarily be administered through another route (inhalation) to treat another disease. *Fink et al.* does not discuss or teach the use of applicant's specific α-keto acids as antioxidants to neutralize hydrogen peroxide in the lungs of mammals to treat bronchial constriction and bronchial spasms.

Applicant submits that contrary to the Examiner's position, the manner of administration of the compound is critical. *Fink et al.* does not teach or suggest the use of compounds for inhalation.

The combination of the primary reference of *Fink et al.* with the secondary reference of *Radhakrishnan et al.* does not disclose applicant's method for treating a pulmonary disease state in mammals by protecting indigenous *in vivo* levels of nitric oxide in mammalian cells during ozone inhalation above ambient levels. Because the primary reference of *Fink et al.* does not teach or suggest applicant's methods, the secondary reference of *Radhakrishnan et al.*, which merely discloses the use of a corticosteroid for the treatment of asthma, adds nothing to the primary reference of *Fink et al.* The combination of *Fink et al.* with *Radhakrishnan et al.* does not disclose applicant's method for treating bronchial constriction/spasm/airway disease in mammals.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 706.02(j)

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972. 973 (Bd. Pat. App. & Inter. 1985). MPEP 706.02(j)

In order for a combination of references to render an invention obvious, it must be obvious that their teachings can be combined. *In re Avery* (CCPA 1975) 518 F2d 1228, 186 USPQ 161. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. *In re Geiger* (CAFC 1987) 815 F2d 686, 2PQ2d 1276; *In re Fine* (CAFC 1988) 5 PQ2d 1596. When the incentive to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper. *Ex parte Skinner* (BPAI 1986) 2PQ2d 1788. The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *Berghauser v. Dann. Comr. Pats.* (DCDC 1979) 204 USPQ 393; *ACS Hospital Systems. Inc. v. Montefiore Hospital* (CAFC 1984) 732 F2d 1572, 221 USPQ 929. Same, where the references expressly teach away from what the PTO contends is obvious from the references. *In re Grasseli et al.* (CAFC 1983) 713 F2d 731, 218 USPQ 769. The references, viewed by themselves and not in retrospect, must suggest doing what applicant has done. *In re Shaffer* (CCPA 1956) 229 F2d 476, 108 USPQ 326, In re Skoll (CCPA 1975) 523 F2d 1392, 187 USPQ 481.

The mere fact it is possible for two isolated disclosures to be combined does not render the result of that combination obvious absent a logical reason of record, which justifies the combination. *In re Regel et al.* (CCPA 1975) 526 F2d 1399, 188 USPQ 136. To properly combine two references to reach a conclusion of obviousness, there must be some teaching, suggestion or inference in either or both of the references, or knowledge generally available to one of ordinary skill in the art, which would have led one to combine the relevant teachings of

the two references. *Ashland oil Inc. v. Delta Resins and Refractories. Inc. et al.* (CAFC 1985) 776 F2d 281, 227 USPQ 657; 5 PQ2d 1532.

It is not proper within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. It is not appropriate to combine the inhalable corticosteroid of *Radhakrishnan et al.* with the orally ingestible ethyl pyruvate of *Fink et al.* The references of record fail to teach or suggest applicant's invention as a whole.

Accordingly, the Examiner's rejection of claims 30 and 33-51 under 35 U.S.C. §103(a) as being unpatentable over *Fink et al.* in view of *Radhakrishnan et al.* should be withdrawn.

Applicant requests that the Examiner consider the above Amendment and Response and pass this application to issue. Applicant requests the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments, which might be most expeditiously handled by a telephone conference. No fee is deemed necessary in connection with the filing of this Amendment and Response. If any fee is required, however, authorization is hereby given to charge the amount of such fee to Deposit Account No. 13-4822.

Respectfully submitted,
Alain Martin

By _____
Richard R. Muccino
Reg. No. 32,538
Attorney for Appellant(s)

Direct communications to:
Richard R. Muccino
758 Springfield Avenue
Summit, New Jersey 07901
voice (908) 273-4988
fax (908) 273-4679

AMERICAN JOURNAL OF
Respiratory Cell and
Molecular Biology

Am. J. Respir. Cell Mol. Biol., Volume 20, Number 5, May, 1999 1067-1072

Cell Injury and Interstitial Inflammation in Rat Lung after Inhalation of Ozone and Urban Particulates

Ian Y. R. Adamson, Renaud Vincent, and Stephen G. Bjarnason

Department of Pathology, University of Manitoba, Winnipeg, Manitoba; and Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Coexposure of the lung to urban dust along with ozone appears to potentiate ozone-induced injury. This conclusion was derived from whole-lung studies involving tissue and lavaged cells, but we now speculate that the injury and inflammatory response at the main site of reactivity, the bronchoalveolar duct region, is underestimated by such whole-lung studies. We exposed rats to ozone at 0.8 ppm and urban particulates (EHC93) at 50 mg/m^3 for 4 h. Animals were killed 33 h later with tritiated thymidine (^{3}HT) injected 1.5 h before death. Lungs were fixed by vascular perfusion to avoid disturbing any epithelial cell changes or local inflammation and edema in the air spaces. Tissue was embedded from central and peripheral areas of the lung, then counts of labeled cells, polymorphonuclear leukocytes (PMN), and macrophages (MAC) were made separately on methacrylate sections. The results showed that epithelial cell injury and regeneration (% of ^{3}HT-labeled cells) was greatest in the ozone plus dust group, and was three times higher in periductal areas than in whole-lung counts. Although some increase in inflammatory cells in the air spaces was found in the coexposure group, much higher numbers of PMN and MAC were counted in the lung tissue compartment, and counts were significantly higher than those found after ozone or dust alone. Values from the latter groups were also higher than those from air controls or samples of distal lung taken from any inhalation group. The results demonstrate that inhalation of an urban dust at a level that causes few lung effects when inhaled alone can potentiate ozone toxicity, particularly in the vicinity of the alveolar duct, where the accumulation of interstitial inflammatory cells may be an important factor in the development of any subsequent pathologic changes.